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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/160,067 | 09/24/1998 | WALTER H. GUNZBURG | GSF98-04A | 5908 |

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| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 18 |

DATE MAILED: 12/21/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/160,067 | Applicant(s) GUNZBURG ET AL. | |
|---|---|---|---|
| | Examiner Sumesh Kaushal | Art Unit 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/01 has been entered.

Claim 5 was canceled.

Claims 1, 9-11, 16 and 22 were amended.

Claims 1-4 and 6-22 were pending and were examined in this office action.

*The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.*

*Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.*

*The references cited herein are of record in a prior Office action.*

Applicant's arguments filed 10/19/01 have been fully considered but they are not persuasive, for the reasons of record as set forth in the earlier office action (Paper No.12, 10/12/00) and new ground(s) of rejection below as necessitated by the recent amendments.

***Double Patenting***

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of co-pending Application No. 09/442,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because "a method of treating a tumor by administering a capsule, which encapsulates a cytochrome P450 expressing cells, wherein the capsule comprises a porous membrane which allows a prodrug molecule to pass into the capsule, wherein the prodrug molecule are converted into active drug molecule by cytochrome P450 either simultaneously or with a time span" as claimed in the instant application is obvious in view of "a method of treating a solid tumor (pancreatic and/or breast) comprising locally administering into the tumor or close to a site of the tumor .... a capsule encapsulating cytochrome P450 producing

cells .....wherein the solid tumor mass is reduced when compared to the solid tumor mass prior to said administration" as claimed in the co-pending application 09/442,979. In addition the method as claimed in the co-pending application 09/442,979 could not be exercised without the capsule as claimed in the instant application. Therefore, the invention as claimed in the instant application is obvious in view of invention as claimed in the co-pending application 09/442,97.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of ablation of tumor cells by introducing the capsule (as claimed) into the tumor, does not reasonably provide enablement for the method as claimed wherein the capsule is contacted with the tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claim recites limitation "contacting said tumor cells with prodrug molecule and a capsule". The scope of instant claim encompasses contacting the tumor cells with a capsule, wherein the capsule has been administered systemically. At best the specification only teaches the direct injection of capsule containing the genetically engineered cells that encodes

p450 into the tumor. The specification fails to disclose that systemic administration of capsules as encompassed by instant claimed would result in the ablation of tumor cells in in-vivo. The specification fails to disclose capsules that falls in the range of encapsulated single cell suspension. It is general knowledge in the art that microparticle administered via systemic circulation would binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. Furthermore, it is unclear how one skill in the art would contact a tumor in the brain by administering the capsules via systemic circulation because blood-brain barrier would prevent any such contact. At best the specification only teaches local injection encapsulated cells (as claimed) into a tumor.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the instant claim. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, for contacting the tumor with encapsulated cells via systemic circulation is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-9, 15-19 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Tai et al (FASEB Journal 7: 1061-1069, 1993) and Merten et al. (Cytotechnology 7(2): Abstract , 1991) in view of Wei et al. (Human Gene Therapy 5: 969-978, 1994).

The applicant argues that applicant's invention is unexpected and Wei and Tai do not render the instant invention obvious, particularly after the recent amendment (response: page 8, ¶3). The applicant argues that Wei does not teach or even suggest the use of capsule for any purpose (response: page 7, ¶3). The applicant further argues that the purpose of encapsulating cells is to immunoisolate the cells so that pore size of the membrane is small enough to prevent components of immune system from entering the capsule. The applicant further argues that one skill in the art would expect that such pore size in the capsule would prevent the entry of prodrugs into the capsule (response: page 8, ¶2-3).

However, this is not found persuasive because applicants argument alone cannot take place of evidence lacking in the record (*see In re Scarbrough 182 USPQ, (CCPA) 1979*). In addition, Tai clearly teaches that appropriate semipermeability is required that allow easy diffusion of secreted gene product without compromising the immunoisolating properties of the membrane (Tai page 1061, col.2). Therefore, one ordinary skill in the art would select the appropriate pore size that facilitates the entry of prodrug molecules.

In addition, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention.

In this case, Tai et al. teaches that sustained delivery of the desired gene product in vivo can be achieved by encapsulating the genetically modified cells in a biocompatible membrane (a capsule). Tai further teaches that microencapsulation delivery overcomes problems associated with somatic gene therapy such as the inability to achieve efficient gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation. Tai et al. further teaches the use of an alginate-poly-L-lysine semipermeable membrane that provided a microenviroment that was physiologically compatible with the growth of the modified cells and allowed easy diffusion of the secreted gene products without compromising the immunoisolating properties of the membrane.

Similarly, Merten et al. teaches a method for encapsulation of mammalian cells using capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride (PDMDAAC). However, Tai and Merten do not teach the encapsulation of genetically engineered cells that produced cytochrome P450.

Wei et al. teach genetically engineered mouse fibroblasts that produces Cytochromoe P450. Wei further teaches that cytochrome P450 2B1 activates the inert prodrug, CPA into its cytotoxic metabolites. In addition, Wei et al. teaches that the transplantation of cytochrome P450 2B1-producing fibroblasts followed by CPA administration, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas.

Thus, it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Tai and Merten who in teaches the encapsulation of genetically

engineered cells to deliver the gene product of interest in vivo, with the teaching of Wei et al who teaches genetically engineered cells that produces p450. One would have been motivated to make a capsule containing genetically engineered cells that produces cytochrome p450 because encapsulation of cells to overcomes problems associated with somatic gene therapy such as the inability to achieve efficient gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation. One would have been motivated to implant encapsulated cells because systemic P450 is known to activate the inert prodrug, CPA into its cytotoxic metabolites, which would then kill cells in the vicinity of the implanted capsule. The would have had a reasonable expectation of success at the time of filing based on the results of Wei et al. who showed that the transplantation of cytochrome P450 2B1-producing fibroblasts to mice brains followed by CPA administration prevented meningeal neoplasia as well as the results of Tai et al. that showed significantly higher levels of human growth hormone from the recipients of encapsulated cells relative to the recipients of unencapsulated cells. In addition, one ordinary artisan would have been motivated at the time of filing to also include in the claimed pharmaceutical kit, the prodrug which is activated by cytochrome P450, in a different form because by supplying both components together as a kit, make their intended use easier. Therefore, invention as claimed is prima facie obvious in view of cited art.

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this

application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED to facilitate further examination.

*S. Kaushal*
**PATENT EXAMINER**

SCOTT D. PRIEBE PH.D
PRIMARY EXAMINER